Renal Transplantation

1933 First cadaveric renal allograft Voronay in Ukraine – 48 hr survival
1951 Azathioprine available for human use
1955 First successful Tx - intertwin renal transfer, Murray 1955 (Boston US)
1962 Corticosteroids with azathioprine
1967 Renal preservation media and pulse preservation
1966 Direct crossmatch introduced
1970s Brain death laws in US and beating heart cadaveric harvesting
1978 Cyclosporin introduced
1980s University of Wisconsin media

Outcomes

	Live donor	Cadaveric donor
Patient survival		
1 year	97.8%	95%
3 year	95.2%	89.2%
5 year	90.5%	81.3%
Allograft survival		
1 year	94.7%	89.2%
3 year	87.4%	77.7%
5 year	76.0%	61.3%

Adverse risk factors

Extremes of recipient age (> 55yrs or < 1 yr)
Extremes of donor age (> 50 yrs or < 2 yrs)
Previous failed transplant
BMI > 30
Diabetes
Blacks
Coronary artery disease
Hypercoagulability
Risk factors for recurrent renal disease (#1 diabetes)*

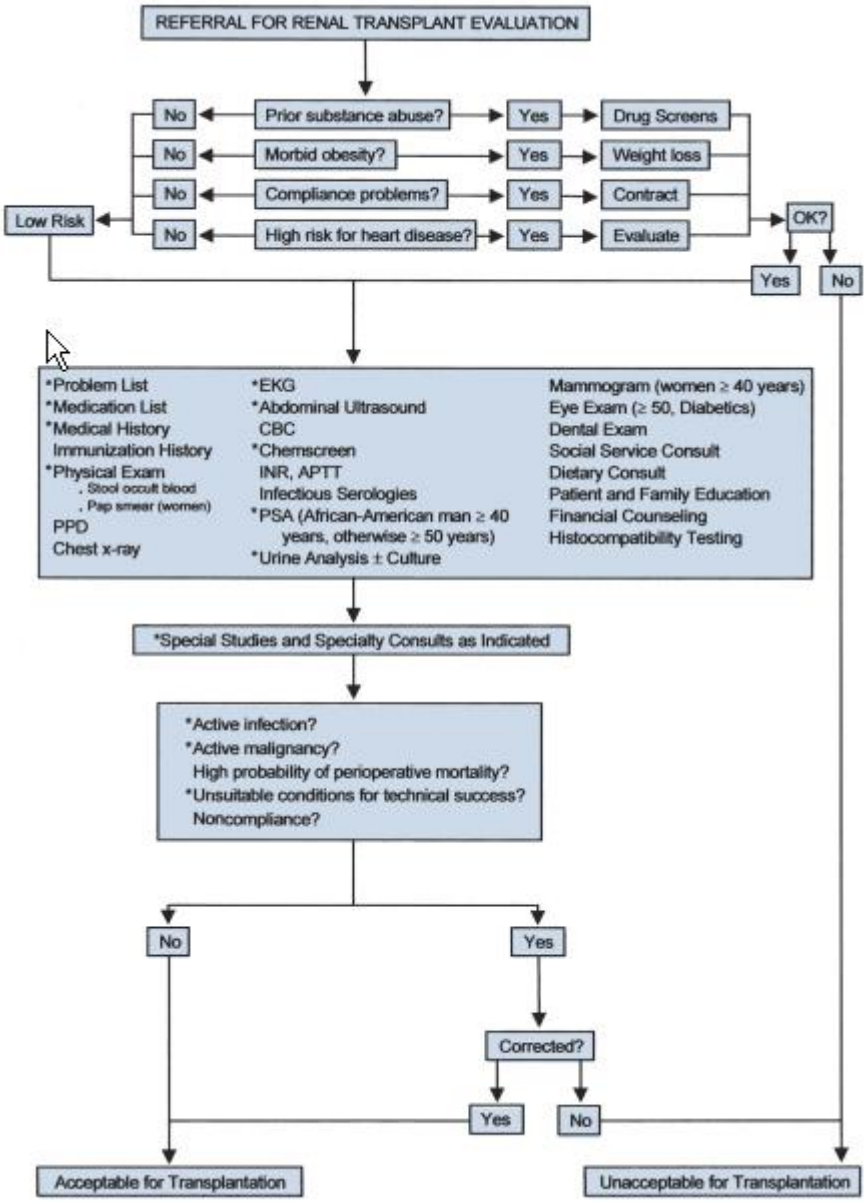
* Systemic or primary renal disease

Systemic Diabetes, HUS, HSP, SLE, cryoglobulins, Wegener's, scleroderma, sickle cell, oxalosis
Renal IgA, membranoproliferative, anti-GBM, focal segmental glomerulosclerosis

NB. HUS, focal segmental glomerulosclerosis and primary oxalosis very high risk of recurrence and graft failure

Recipient evaluation

Confirm irreversible renal failure
Exclude significant systeic medical disease (including infection)
Exclude active malignancy or treated cancer with high risk of relapse
Exclude substance abuse or ongoing uncontrolled psychiatric disease



Serological testing:	HBV, HCV, CMV, syphillis, EBV, HSV, HIV, HTLV-1, Toxoplasma, TB, VZV
Vaccination:	Pneumococcus (if < 6yrs) Influenza Hepatitis B (0, 1 and 6 months pre-op) Varicella zoster (if seronegative) Tetanus diptheria toxoid Polio booster MMR
Cancer:	Disease-free intervals of 2-5 years recommended

	Shorter for individual cancers ? low risk RCC
	No wait for skin cancers and CIS cervix or primary brain tumours
	Cholecystectomy for gallbladder polyps > 1cm
Urological:	History to exclude dysfunctional voiding
	Urinalysis to exclude infection/microhaematuria
	USS and postvoid residual to exclude hydro and poor emptying
	TURP/BNI may be required
	Diversion not necessarily a contraindication: transplant into pouch/conduit reportedly succesful
	Biopsy to exclude fibrosis +/- wet augment recommended for patients diverted for reflux – capacity rapidly returns to normal in absence of fibrosis (pre-Tx Nx usually required)
Other:	ADPKD = cerebral aneurysm screening
	Peripheral arterial or venous disease = dopplers

<u>Indications for pre-transplant nephrectomy (Campbells)</u>

Renal stones not cleared by minimally invasive techniques or lithotripsy

Solid renal tumors with or without acquired renal cystic disease

Polycystic kidneys that are symptomatic, extend below the iliac crest, have been infected, or have solid tumors

Persistent antiglomerular basement membrane antibody levels

Significant proteinuria not controlled with medical nephrectomy or angioablation

Recurrent pyelonephritis

Grade 4 or 5 hydronephrosis

S	Stone
T	Tumour
I	Infection
M	Massive
P	Proteinuria
4	Grade 4/5 reflux

<u>Contraindications to renal transplantation</u>

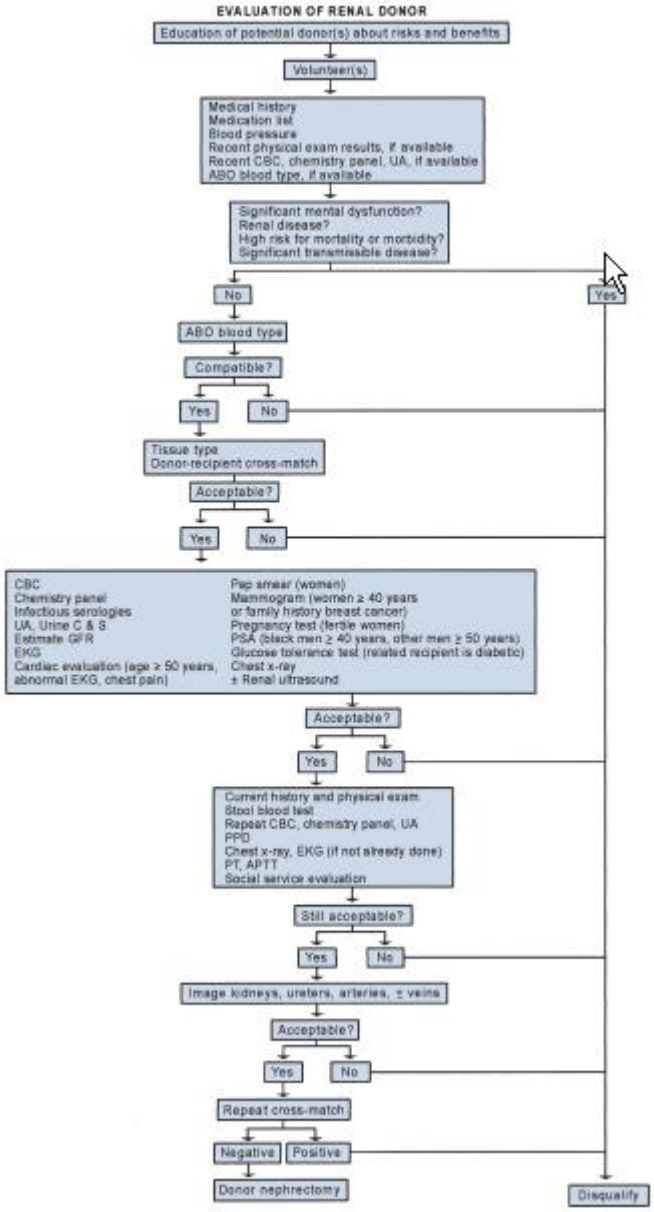
Active systemic renal disease (SLE, anti-GBM, HUS, ANCA + GN)
Oxalosis (combined renal and liver transplant)
Active infection
Recently treated or uncontrolled/disseminated malignancy
Prohibitive extrarenal disease (CVS etc.)
Active IV or alcohol abuse
Non-compliance
Uncontrolled psychiatric disorder

M	Malignancy
I	Infection
N	Nephropathy
C	Compliance issues

E Severe extrarenal disease
S Substance abuse
O Oxalosis
P Psychiatric disorder

Living donor evaluation

Exclude renal disease
Exclude active infection
Exclde transmissible malignancy



Best kidney left behind: ~ 80% CrCl achieved post-op – hyperfiltration leads to IL-10 production and TGF-B release.
If both equal choose right side in female of childbearing age
Imaging of choice = 3D CT angiography with delayed images best modality to image arteries, veins and drainage
Most living donor allografts now harvested laparoscopically – cuff of IVC on R

Typically mannitol given prior to renal vessel clamping (diuresis/free-radicals)
Overall:

Morbidity	1.8-7% general complications (cardiac, thrombotic, lungs) Slightly increased risk of HT and proteinuria vs. general population but clinically insignificant 0.1% risk of ESRF long-term
Mortality	0.02%

Cadaveric donors

Beating heart donors with clinically determined brain stem death
Similar criteria to above re. malignancy, active infection etc.
Age 6 – 50 yrs acceptable
Low numbers resulted in 'extended criteria', but graft survival poorer in those younger than 6 or older than 50. Young donor kidneys can be used as pairs 'en bloc' with attached IVC & aorta. Also Light criteria utilising biopsy findings and clinical criteria used to predict risk of transplant failure
Always go for left-side if possible and single renal vessels.

Organ preservation after procurement

Warm ischaemia – failure of oxidative phosphorylation - ATP depletion – Na/K pump failure – intracellular Na accumulation – cell swelling – no-reflow after revascularisation. Also free-radical production via hypoxanthine
Cold ischaemia reduces energy requirements dramatically
2 methods: Simple cold slush storage (UoW)
Pulsatile perfusion

(i) Cold slush storage

Good kidneys
Storage up to 48 hours at 4'C
Cold ischaemia times > 24 hours a/w higher incidence of delayed graft function. Recommendation <21 hours.
University of Wisconsin solution – better vs. Eurocollins (Ploeg 1992)
UoW consituents

a. Lactobionate, starch, raffinose – HMW solutes limit sweling
b. Phosphate – buffer H+ ions
c. Adenosine – substrate for ATP synthesis
d. Glutathione – free-radical scavenger
e. Allopurinol – inhibits xanthine oxidase and free-radicals
f. Mg and DXM – membrane stabilisers
g. Penicillin – antibiosis
h. Insulin

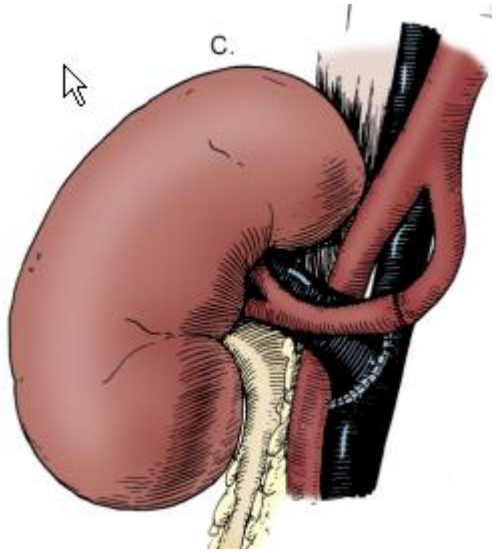
(ii) Pulsatile perfusion

Poor kidneys (elderly donors, marginal criteria)
Allows assesment of flow (> 100ml/min), pressure (<40/25 mmg) and resistance (<0.3) features required for Tx

Transplantation – operative technique

Bench table vascular reconstruction important in cadaveric and LD Nx
- lap – removal of staple lines and construction of single venous and arterial channels if necessary
- cadaver – use of IVC to lengthen renal vein on right. Construction of single vessel channels

Give antibiotics, steroids and immunoglobulins at induction
Typically RIF – external iliac vein more superficial cf. left
Extraperitoneal approach favoured in UK (avoids intestinal complications, ease of biopsy, confines surgical mischief)
Rutherford-Morrison type incision pubic symphysis to point 4 fingers above ASIS. Preservation of vas, division of round ligament and inferior epigastric. Mobilisation of peritoneum medially. Heparin given before vessel clamping. mannitol at time of anastomosis. End-to-end arterial anastomosis first from renal artery to either hypogastric artery or end-to-side to external iliac artery. Then venous anastomosis external iliac (arterial anastomosis more critical and reduces external iliac clamping time). Lastly extravesical antirefluxing ureteroneocystostomy (transvesical or extravesical) – Lich Gregoir in UK vs. Leadbetter-Politano in US (higher incidence of reflux in UK but lower incidence of bladder dysfunction).



Post-operative complications

Early and late transplant-related complications and long-term non-surgical complications of renal transplantation.
Surgical complications causing allograft dysfunction divided into renal, vascular or urological complications:

A. Early allograft dysfunction
- Renal
  - Acute tubular necrosis*
  - Prolonged cold ischaemia time and reperfusion injury*
  - Acute rejection (see below)
  - Acute cyclosporin toxicity
- Vascular

Venous thrombosis
Arterial occlusion
Haemorrhage
AV fistula

Urological
Urine leak or fistula
Urinary obstruction

* Leads to delayed graft function, defined as the need for dialysis in the first week after Tx
The above are investigated by allograft USS with Doppler, cyclosporin levels and if necessary, renal biopsy

B. Late allograft dysfunction

Renal
Chronic rejection
Chronic cyclosporin toxicity

Vascular
Renal artery stenosis

Urological
Urinary tract obstruction
UTI
Urinary stones

C. Medical consequences of renal transplantation

Coronary artery disease
Diabetes
Malignancy
Reproductive

<u>Allograft rejection</u>

Hyperacute, accelerated, acute and chronic:

(i) Hyperacute
Very rare
Immediate to 24 hours post-Tx
Pre-formed cytotoxic antibodies to allograft MHC – should not occur in absence of negative compatability screening
No Rx – nephrectomy required

(ii) Accelerated
Rare
Up to 10 days post-Tx
Primary immune response – humoral and cell-mediated
Very aggressive and difficult to treat – may result in graft rupture
Less common with anti-lymphocyte induction therapy

(iii) Acute
Common – up to 50% of transplants
Up to 6 months post-Tx
Raised serum creatinine +/- systemic flu-like symptoms, graft tenderness and hypertension
Cause unknown – diagnosed on biopsy after exclusion of infection

Typically lymphocytic infiltrate around tubules and vessels - severity graded by Banff criteria
Usually amenable to corticosteroid anti-rejection Rx (+ antilymphocyte agents if no response at 48 hrs)

(iv) Chronic
Common
Used to be called chronic allograft rejection – now IFTA (interstitial fibrosis and tubular atrophy)
Progressive decline in renal function leading to failure
Thought due to repeated immunological insults/toxicity due to immunosuppressive medications
Typically intimal proliferation and interstitial fibrosis – relative absence of lymphocytic infiltrate cf. acute rejection (can be difficult to differentiate from chronic cysclosporin toxicity)
No specific Rx – limitation of other insults (DM etc.)

<u>Vascular complications</u>

Renal artery stenosis
1-15% incidence
Due to surgeon error (narrowing, kink), arteriosclerosis, fibrosis
Typically presents with poorly controlled HT +/- bruit
> 70% stenosis >15mmHg gradient
Suggested by Doppler, ACEI renography, angiography (best)
Rx = angioplasty: outcome for surgery poor

Renal artery thrombosis
Rare <5%
Surgeon error – intimal flap or kink
Diagnosed on Doppler (no flow) or renogram (photopenia)
Rarely salvageable – Nx

Renal vein thrombosis
Rare
Technical error, haematoma, iliofemoral DVT, pro-thrombotic state,
Diagnosed on renogram (background scintillations) or Doppler (reversal of venous flow)
Rx = Thrombolysis/thrombectomy, Nx common

<u>Urological complications</u>

Infection

Stones

Urinary obstruction (3%)
Early (haematoma, urinoma, lymphocoele, surgeon error) or late (ischaemia or fibrosis, stone, tumour, bladder pathology)
Non-contrast imaging and standard endourological Mx
Most ureteric strictures due to ischaemia – exacerbated by BK virus

Fistula (2-3%)
Usually due to devascularisation, ischaemia and necrosis
Typically distal third ureter (all supply from allograft renal artery)

Rx small leaks	conservative with stent
Rx large leaks/ necrosis	reconstruction options: Allograft – native ureteroureterostomy

Allograft – native pyeloureterostomy
Allograft – native calicoureterostomy
Calicocystostomy
Boari flap +/- psoas hitch
Ileal interposition

Lymphocoele
- 0.5 – 20% incidence
- Asymptomatic; occasionally graft dysfunction or LUTS
- Often recur following aspiration – open or lap marsupialisation vs. aspiration and cavity sclerosis

<u>Medical consequences</u>

Post-transplant diabetes
- Incidence 3.4 – 46%
- Generally due to corticosteroids; also reported with cyclosporin and tacrolimus; often settle
- 3 wks to 19 yrs post-transplant
- Non-insulin or insulin-dependent
- Worse patient and graft survival

Malignancy

Post-transplant lymphoproliferative disease*	~ 2-3 yrs
Kaposi's sarcoma	~ 2-3 yrs
Squamous carcinomas (skin, cervix, vulva and anus)	~8-10 yrs

- All above occur with greater frequency in transplant popn. Due to combination immunosuppression
- No difference for lung, breast, prostate, colon or uterine, but earlier onset and more aggressive
  - PSA levels normal in renal failure
  - Cytology reliable in transplant patients
  - BCG OK but increases risk of sepsis
- Urothelial cancer risk slightly increased due to BK virus (decoy cells on cytology, diagnosed with blood and urine PCR – Rx reduce immuno-suppression, Rx urothelial tumour)
- *PTLD
  - ~1% of renal transplants
  - Not the same as NHL
  - A/w Epstein Barr virus
  - Aggressive vs. normal
  - Multicentric and extra-nodal
  - CNS and allograft involvement relatively common

*EBV infection
- Increased risk of post-transplant lymphoproliferative disease
- EBV viraemia on PCR
- Reduce immunosuppression and give Rituximab (if CD25 positive)

CMV infection
- Lethargy, respiratory symptoms and hepatitis
- Destauration on mobilisation
- Ground glass appearance on CXR
- Serology and PCR reaction for diagnosis
- Screen donor and recipient
- 3 months prophylaxis with septrin

- Valgancicylovir and for Rx; foscarnet for resistance

Reproductive

- Male infertility
  - Sperm parameters improve following Tx but not to normal levels – many cases of pregnancy reported
  - Serum T and FSH/LH usually normalise following Tx suggesting improved Leydig cell function in non-uraemic state
- Pregnancy
  - Possible but increased risks of pre-eclampsia (25%), pre-term labour (~50%) and neonatal morbidity (30%)
  - Graft function deteriorates in pregnancy, with 5-10% cases developing permanent graft dysfunction
  - No evidence that graft position impairs foetal delivery
  - Chromosomal aberrations higher in offspring but no definite increase in haematological malignancy
  - Attempts at pregnancy generally allowed after ~12 months

Appendix

Histocompatability

ABO blood groups and major histocompatability complex (MHC)

(i) ABO blood groups

Blood antigens (eg. A and B) present on endothelial cells in transplant kidney – recipient blood contains antibodies to antigen they lack

Cross match crucial to assess compatibility

Occasionally A2 kidneys transplanted into O or B donors with low anti-A2 antibodies

(ii) MHC antigens

Encoded by MHC genes on short arm chromosome 6

Glycoproteins on cell membrane of all cells:

Class 1 MHC antigens	All nucleated cells HLA-A, HLA-B. HLA-C Bind 8-10 amino acids in groove Interacts with CD8 Subtype detected by tissue typing T lymphocytes
Class 2 MHC antigens	B and activated T lymphocytes and antigen presenting cells HLA-DR, HLA-DQ, HLA-DP Bind 12-28 amino acids in groove Interacts with CD4 Subtype detected by tissue typing B lymphocytes

Huge variation in HLA/MHC gene polymorphisms (see below) allows humans as a species to respond to a myriad of potential pathogens

HLA SPECIFICITIES

A	B	B	C	DR	DQ	DP
A1	B5	B51(5)	Cw1	DR1	DQ1	DPw1
A2	B7	B5102	Cw2	DR103	DQ2	DPw2
A203	B703	B5103	Cw3	DR2	DQ3	DPw3
A210	B8	B52(5)	Cw4	DR3	DQ4	DPw4
A3	B12	B53	Cw5	DR4	DQ5(1)	DPw5
A9	B13	B54(22)	Cw6	DR5	DQ6(1)	DPw6
A10	B14	B55(22)	Cw7	DR6	DQ7(3)	
A11	B15	B56(22)	Cw8	DR7	DQ8(3)	
A19	B16	B57(17)	Cw9(w3)	DR8	DQ9(3)	
A23(9)	B17	B58(17)	Cw10(w3)	DR9		
A24(9)	B18	B59		DR10		
A2403	B21	B60(40)		DR11(5)		
A25(10)	B22	B61(40)		DR12(5)		
A26(10)	B27	B62(15)		DR13(6)		
A28	B2708	B63(15)		DR14(6)		
A29(19)	B35	B64(14)		DR1403		
A30(19)	B37	B65(14)		DR1404		
A31(19)	B38(16)	B67		DR15(2)		
A32(19)	B39(16)	B70		DR16(2)		
A33(19)	B3901	B71(70)		DR17(3)		
A34(10)	B3902	B72(70)		DR18(3)		
A36	B40	B73		DR51		
A43	B4005	B75(15)		DR52		
A66(10)	B41	B76(15)		DR53		
A68(28)	B42	B77(15)				
A69(28)	B44(12)	B7801				
A74(19)	B45(12)	B81				
A80	B46	Bw4				
	B47	Bw6				
	B48					
	B49(21)					
	B50(21)					

However, makes life difficult when trying to find compatible matches

Detecting incompatability

Originally complement dependent cytotoxicity (CDC) used, utilising donor lymphocytes and recipient sera in direct tests, with rabbit complement to stimulate cell lysis. However dependent on complement pathways and not that sensitive or specific.

Flow cytometry or ELISA based tests (known as panel reactivity antibody testing (PRA)) have now become standard to give an indication of the likelihood of chronic rejection. However ultimate decision to use kidney based on HLA compatibility. In general matching at only 3 loci; HLA-A, HLA-B and HLA-DR:

000 full house match

222 complete mismatch

Low risk	000 or single mismatch at non-DR locus
Medium risk	2B mismatches or 1DR mismatch
High risk	2DR mismatch, 2nd transplant

Life of transplant related to degree of match:

HLA Antigens Mismatched	No.	Half-Life (Yr) [*]
0	4,182	15
1–3	9,391	12
4–6	14,186	10

Before transplantation a manual XM is performed between recipient serum and donor lymphocytes in all cases to exclude hyperacute rejection

Living-related donors (see below)

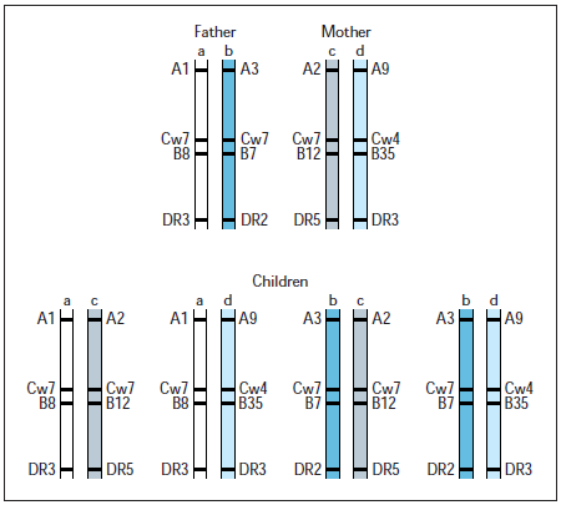
Each individual has 2 x chromosome 6

Parent shares 50% chromosomes with child

Siblings

25% chance of perfect match or mismatch

50% chance of 'half-match'



Immunology of graft rejection

Recognition of allograft as foreign occurs in two ways: direct recognition of donor APCs and recipient processing of donor peptides by host APCs (indirect recognition)

Activation of T-cells requires 3 signals: anigen presentation, glycoprotein binding (CD28 etc.) and IL-2. IL-2 require to provide co-stimulatory signal to drive cytotoxicity. Killing mediated in three ways: cytotoxic T-lymphocytes, antibody mediated (complement activation, opsonisation), delayed type hypersensitivity

Immunosuppresive therapy and side effects

A. Induction therapy designed to prevent rejection in first 3 months

IL-2 receptor antagonist (basiliximab)	anti B-cell
Anti-thymocyte globulin	anti T-cell*
Adeluzumab	anti B and T-cell

* very toxic and requires central line – only for high risk induction

B. Chronic anti-rejection therapy

Typically triple therapy:

(i) calcineurin inhibitor
cyclosporine, tacrolimus

(ii) purine inhibitor
azathiaprine, mycophenolate mofetil

(iii) steroids

Combination of above depends on risk of rejection (see above) – each nephrology unit has own protocols. Typically:

Low risk	cyclosporine, azathiaprine, steroid
High risk	tacrolimus, mycophenylate mofetil, steroid

Recently rapamycin used alone or in combination with cyclosporine in an attempt to reduce steroid intake

Pulsed steroids for acute rejection; anti-lymphocyte agents for non-responders

NB. Cyclosporin and tacrolimus metabolised by cytochrome p450 system – inhibitors increase dose (ABx except anti-TB drugs; Ca-channel blockers); inducers reduced dose (anti-TB ABx; epilepsy drugs)

Immunosuppressant	Mechanism of Action	Interferes with...
Glucocorticoids	Reduce transcription of cytokine genes	Intracellular signaling
Azathioprine	Inhibits purine synthesis	Lymphocyte proliferation
Mycophenolate mofetil	Inhibits purine synthesis	Lymphocyte proliferation
Sirolimus	Inhibits cell cycle progression	Lymphocyte proliferation
Tacrolimus	Inhibits calcineurin and interleukin-2 production	Intracellular signaling
Cyclosporine	Inhibits calcineurin and interleukin-2 production	Intracellular signaling
Monomurab CD3	Depletes T lymphocytes	Antigen recognition
Equine antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Rabbit antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Alemtuzumab (off label)	Depletes T and B lymphocytes	Antigen recognition and antibody production
Rituximab (off label)	Depletes B lymphocytes	Antibody production
Basiliximab	Blocks interleukin-2 receptor	Intercellular signaling
Daclizumab	Blocks interleukin-2 receptor	Intercellular signaling

Side Effects of Immunosuppressive Medications

Corticosteroids
- Diabetes
- Lipid disorders
- Cushingoid features
- Obesity
- Poor wound healing
- Avascular necrosis (bone)
- Cataracts
- Hypertension, coronary artery disease (CAD)
- Peptic ulceration, gastritis, bowel perforation
- Growth retardation
- Pancreatitis

Cyclosporine
- Nephrotoxicity
- Hypertension, CAD
- Hyperkalemia
- Hyperuricemia
- Heptatotoxicity
- Hirsutism
- Gingival hyperplasia
- Tremors/seizures
- Pancreatitis
- Hemolytic-uremic syndrome

Mycophenolate Mofetil (CellCept)
- Leukopenia
- Gastrointestinal disturbances
- GI bleeding, diarrhea, ulceration, esophagitis, gastritis

Azathioprine
- Bone marrow suppression (pancytopenia)
- Gastrointestinal disturbances
- Hepatotoxicity
- Hair loss

Antilymphocytic agents

Polyclonal
- Fever, chills
- Leukopenia, thrombocytopenia
- Serum sickness
- Local phlebitis

Monoclonal
- Flulike syndrome:
- Fever, chills, tremors, headache, nausea, vomiting, and diarrhea
- Aseptic meningitis
- Hyptotension
- Pulmonary edema

FK506 (Prograf/Tacrolimus)
- Nephrotoxicity
- Diabetes
- Neurotoxicity

Interleukin Inhibitor
- Simulect

Rapamune (Rapamycin)
- Bone marrow suppression
- GI toxicity
- Skin rash
- Hyperlipidemia

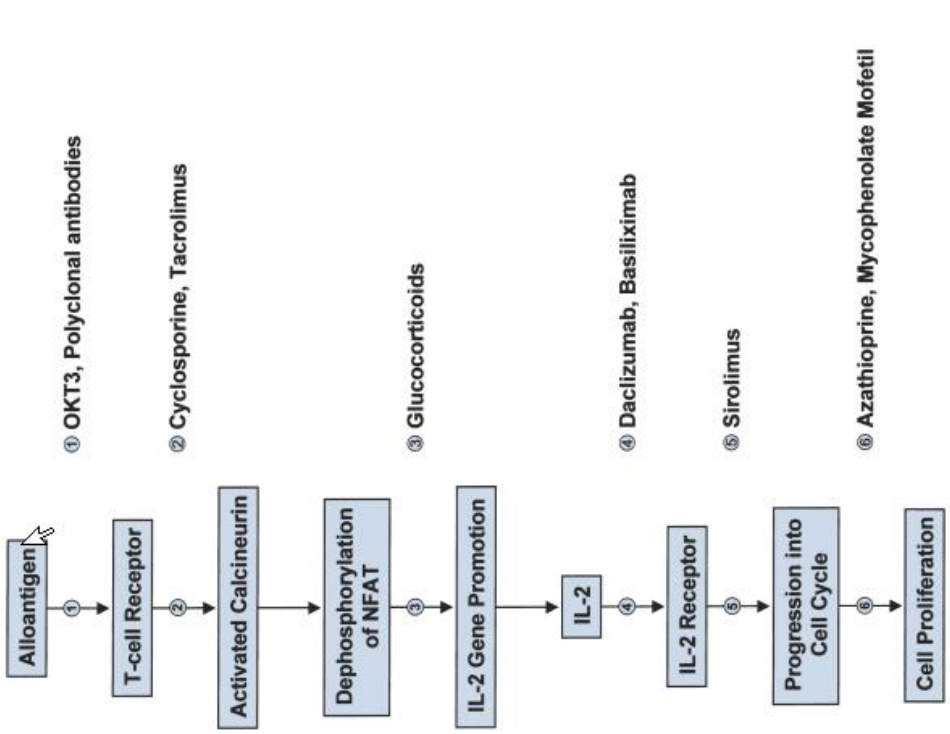


Figure 40-12 Sites of action of commonly used immunosuppressants. IL-2, interleukin-2; N

Basic immunology

Innate
NK cells
Complement
Acute phase proteins
Physical and mucosal barriers

Acquired

MHC class I antigens	HLA A, B and C
	All nucleated cells, including T-cells
	Interact with CD8 on immune cells
MHC class II antigens	HLA DR, DP, DQ
	Antigen presenting cells
	Macrophages
	Monocytes
	Some B cells
	Langerhan's skin cells
	Dendritic cells
	Vascular endothelial cells
	Interact with CD4 receptor on T-cells
Antigen presentation	Occurs in peripheral lymph nodes
	APCs interact with T-cells

Immune activity vs. infections
Innate and acquired

Extracellular bacteria	Complement killing
	NK activity
	Opsonisation and macrophage killing
Intracellular bacteria	T-cell activation required

Immune activity vs. tumours
Tumours are antigenic, but evade immune mediated killing in a number of ways:

- Downregulation in MHC class I and II
- Decreased expression of transporter antigen proteins (TAPs)
- Overexpression of TGF-B